

Attorney Docket No.: **DC-0261US.NP**
Inventors: **Foote and Yeo**
Serial No.: **10/553,585**
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REMARKS

Claim 4 is pending in the instant application. Claim 4 has been rejected. Claim 4 has been amended. Reconsideration is respectfully requested in light of the amendments to claim 4 and the following remarks.

I. Rejection of Claims Under 35 U.S.C. 102

Claim 4 has been rejected under 35 U.S.C. 102(e) as being anticipated by Zoghbi et al. (US Patent Application 2004/0243010). The Examiner suggests that this reference discloses a method of determining the level of B-type natriuretic peptide (BNP) in a plasma sample from a patient prior to exercise to establish a baseline and also determining the level of BNP in a sample from the patient post exercise, as well as teaching that the exercise stress test can be performed with myocardial perfusion imaging wherein the dual isotope, rest-stress protocol is used. The Examiner further suggests that the clause starting with "wherein" in the claims does not limit the invention as it does not recite any additional active steps. Applicants respectfully traverse this rejection.

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At the outset, in order to advance the prosecution and facilitate allowance of the claim, Applicants have amended claim 4 to more clearly define the method of the present invention. Claim 4 as amended recites a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picrogram per milliliter of blood levels of a natriuretic peptide in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and wherein an increase in the actual picrogram per milliliter of blood level of the natriuretic peptide of as small as 9 is indicative of cardiac ischemia in the individual. Support for these amendments to the claim can be found throughout the specification as filed but in particular at pages 9-10 and Table 6 where data are provided showing that the method of the present invention is based on measurement of actual picrogram per milliliter of blood levels. In Table 6, the data gathered using the method of the present invention are shown to be both sensitive and specific with a high level of diagnostic accuracy.

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as compared in particular to ECG changes, with a BNP change of no more than 9 pg/ml useful for diagnosis.

Zoghbi et al. (US2004/0243010) disclose use of an entirely different endpoint for assessing risk of ischemia in patients. As taught Example 7, page 10 of the application, although BNP increased from baseline to immediately post-exercise in individuals with ischemia as well as those without ischemia, the application also teaches that the absolute levels of BNP in blood did not differ between such individuals (see paragraphs [0104] and [0105]). The application states "Neither the absolute BNP levels at peak nor the absolute level of rise from baseline to immediate post-exercise differentiated between ischemic and non-ischemic patients." [see paragraph [0104]]. This teaching by zoghbi et al. is the exact opposite of the results of the specification as filed where in Table 6 it is taught that actual increase in the levels of BNP in blood (greater than 9 pg/ml) are diagnostic of ischemia. As a result, the application of Zoghbi teach away from the method of the present invention which relies on measurement of actual levels of natriuretic peptides in blood, not percent increases as is used by Zoghbi et al. MPEP 2131 states that in order to anticipate an invention the cited

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reference must teach each and every limitation of the claims. As discussed *supra*, the cited reference fails to teach the use of actual picrogram levels of a natriuretic peptide in blood as a measure of ischemia. Accordingly, the reference fails to teach or suggest the limitations of the claims as amended and withdrawal of this rejection is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. 103(a)

Claim 4 has been rejected under 35 U.S.C. 103(a) as being unpatentable over Valkirs et al. (US Patent Application 2003/0109420; hereafter referred to as the '420 application), in view of DeVito (U.S. Patent No. 5,249,124, hereafter referred to as the '124 patent). The Examiner suggests that the '420 application discloses a method of diagnosing myocardial ischemia in a patient by determining a level of BNP in a sample isolated from the patient, including before and after a stress test and that if the test sample is greater than the control sample, then the diagnosis of myocardial ischemia is made. The Examiner suggests that it would have been obvious for one of ordinary skill in the art to incorporate a stress test with myocardial perfusion studies as taught by the '124 patent into the method

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of the '420 application because the '420 application teaches a generic method with respect to a stress test and the '124 patent teaches that such studies provides two images of the heart and the relationship between those images shows heart muscle affected by arteriosclerosis and where it is infarcted. The Examiner further suggests that the clause starting with "wherein" in the claims does not limit the invention as it does not recite any additional active steps. Applicants respectfully traverse this rejection.

As discussed *supra*, Applicants have amended claim 4 to recite a method for detecting cardiac ischemia in an individual suspected of suffering from ischemic cardiovascular disease that comprises measuring actual picrogram per milliliter of blood levels of a natriuretic peptide in blood samples from an individual both before and after the individual has completed an exercise stress test with myocardial perfusion imaging wherein a dual isotope, rest-stress protocol is used, and wherein an increase in the actual picrogram per milliliter of blood level of the natriuretic peptide is indicative of cardiac ischemia in the individual. Support for these amendments to the claims can

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be found throughout the specification as filed but in particular at pages 9-10 and Table 6.

The '420 application discloses measuring levels of BNP in patients as a way to diagnosing myocardial ischemia in the patient. Review of the specific teaching in the application, however, reveals a key difference between the teachings of the '420 application and claim 4 as amended. The method of the '420 application depends on the measurement of absolute thresholds for BNP in blood. As is taught at pages 31-32, baseline levels of BNP correlate with past medical history, where "higher quartile BNP levels" were associated with cardiovascular diseases that included congestive heart failure, renal function, and ECG changes. Then at pages 39 and 40, the '420 patent teaches in various claims that the "threshold BNP level is at least" values such as 60 pg/ml or 80 pg/ml. Nowhere does this patent teach or suggest that an increase in a baseline level of BNP in a patient following a stress test of any type of only 9 pg/ml would be useful for diagnosis of ischemia in a patient.

Moreover, the '124 patent discloses only the use of multi-isotope imaging for myocardial perfusion studies. Therefore,

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this patent fails to overcome the deficiencies in teaching of the '420 application with respect to the claim as amended.

MPEP 2143 states that in order to establish a *prima facie* case of obviousness the references cited and combined must teach the limitations of the claims. As discussed *supra*, the cited references fail to teach the limitations of the claim as amended which recites an increase of as small as 9 pg/ml of a natriuretic peptide in blood as being indicative of ischemia in a patient when levels are measured in the patient both before and after an exercise stress test with myocardial perfusion imaging where a dual isotope, rest-stress protocol is used. Accordingly, the references, either when combined or alone fail to teach or suggest the limitations of the claim as amended and withdrawal of this rejection is respectfully requested.

III. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

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favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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